

Lack of association between the development and clinical course of Type 1 and Type 2 Diabetes Mellitus and rare T130I variant of the *HNF4A* gene in the Polish population

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Abstract

Type 2 diabetes (T2DM) is a multifactorial disease related to both environmental and genetic factors. While environmental factors leading to the development for T2DM are well established, the majority of factors responsible for the genetic background of the disease remain unknown. The aim of this study was to test whether a rare variant within the *HNF4A* gene, Thr130Ile (rs1800961), may influence the development of clinical course of T1DM or T2DM subjects. The analysis included 574 patients with T2DM, 207 T1DM individuals and 284 healthy controls. All subjects were genotyped for the Thr130Ile polymorphism in *HNF4A*. For T2DM, no differences were found in allele frequencies between cases and controls. The percentage of CT genotype in these groups were 5.7% (33 patients) and 5.6% (16 healthy controls), respectively ($p=0.89$). For T1DM, the allele frequency was not statistically different from T2DM or control subjects. In conclusion, no association was found between rare variant Thr130Ile of the *HNF4A* gene and the development of either T2DM nor T1DM in the Polish population.

Key words

diabetes, *HNF4A*, Thr130Ile variant

INTRODUCTION

Type 2 diabetes (T2DM) is a multifactorial disease related to both environmental and genetic factors. While environmental factors leading to the development for T2DM are well established, the majority of factors responsible for the genetic background of the disease remain unknown. In the last few years, research concerning genetic factors leading to the development of T2DM has been mainly related to the common single nucleotide variants (SNVs). However, these mutations only account for a small fraction of the total genetic susceptibilities to T2DM [1]. The potential cause(s) of the missing heritability in SNV-oriented genome-wide association studies (GWAS) is unclear, but possible contributors may include rare gene variants [1]. The hepatocyte nuclear factor 4- α (*HNF4A*) gene codes for the transcription factor, is responsible for regulating gene transcription in pancreatic beta cells, in addition to its primary role in regulation of hepatic genes [2]. Mutations in *HNF4A* may cause maturity onset diabetes of the young (MODY) form of diabetes [2]. *HNF4A* may be considered an interesting candidate gene for T1DM, since *HNF4A* protein regulates endoplasmic reticulum stress-induced apoptosis in pancreatic β -cells [3]. The role of common variants of *HNF4A* in modifying the risk of development of T2DM remains unclear [1, 4]. However, it has been shown that rare variants within *HNF4A* may contribute to the development of T2DM [5].

OBJECTIVE

The aim of this study was to test whether a rare variant within the *HNF4A* gene, Thr130Ile (rs1800961), may influence the development of clinical course of T1DM or T2DM subjects.

MATERIALS AND METHOD

The study included 574 patients with T2DM, 207 T1DM individuals and 284 healthy controls. All patients were residents of southern Poland. DNA of the examined individuals was isolated from the lymphocytes of peripheral blood using QIAamp DNA Mini Kit (Qiagen). All subjects were genotyped for the Thr130Ile polymorphism in *HNF4A* by Taqman allelic discrimination assays and sequencing (TaqMan[®] Gene Expression Assays, Thermo Fisher Scientific Inc., Carlsbad, CA, USA).

All study subjects gave informed consent. The project was approved by the local Ethics Committee (KBET/292/B/2011) and was conducted in accordance with the Declaration of Helsinki. For statistical analysis, tests for differences between the two groups was performed with Student t-test or Mann-Whitney U-test. For categorical variables, either chi-square test or Fisher exact test were used where appropriate. Differences in patient age and time span from age of diagnosis to the age when insulin therapy was necessary between genotypes were assessed with Kruskal-Wallis test.

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RESULTS

Clinical characteristics of the studied population divided into genotypes is summarized in Tables 1–3. For T2DM, no differences were found in allele frequencies between cases and controls. The percentages of CT genotype in these groups were 5.7% (33 patients) and 5.6% (16 healthy controls), respectively ($p=0.89$). No TT genotype was found in either group. Among patients with T2DM, no association was found between genotype and age of diagnosis ($p=0.60$), nor between genotype and time span from age of diagnosis to the age when insulin therapy was necessary ($p=0.75$) (Tab. 4).

For T1DM, the allele frequency was not statistically different from T2DM or control subjects (CT genotype frequency: 2.4% (5 patients), $p = 0.1$), there was also no association between genotype and the age of diagnosis ($p=0.89$) (Tab.5).

Table 1. Clinical characteristics of patients with type 2 diabetes divided into genotypes

T2DM		
	CC	CT
N	541	33
Male	276	17
Female	265	16
Age ⁺	58.4 ± 10.2	58.8 ± 10.2
Age at diagnosis ⁺	48.4 ± 9.8	47.3 ± 9.8
Duration of illness ⁺	10.1 ± 7.7	12.2 ± 6.9
BMI		
<25 kg/m ²	56 (10.9 %)	1 (3.1%)
25-29 kg/m ²	158 (30.6%)	14 (43.8%)
>30 kg/m ²	302 (58.5%)	17 (53.1%)
Insulin		
YES	310 (60.0%)	15 (50.0%)
NO	207 (40.0%)	15 (50.0%)

Mean values ± SD; + – years

Table 2. Clinical characteristics of patients with type 2 diabetes divided into genotypes

T1DM		
	CC	CT
N	202	5
Male	22	2
Female	180	3
Age ⁺	29.2 ± 5.6	30.2 ± 6.5
Age at diagnosis ⁺	17.8 ± 8.1	16.8 ± 7.7
Duration of illness ⁺	11.3 ± 7.4	10.6 ± 12.4%

Mean values ± SD; + – years

Table 3. Clinical characteristics of the control group divided into genotypes

CONTROLS		
	CC	CT
N	268	16
Male	106	7
Female	162	9
Age ⁺	48.6 ± 14.7	43.6 ± 13.3

Mean values ± SD; + – years

Table 4. Age of diagnosis vs genotype in T2DM patients

	CT	CC	p-value	OR (95 %CI)
% of genotypes	T2DM 33 (5.7%)	541 (94.2%)	0.89	1.02 (0.55-1.89)
	Control 16 (5.6%)	268 (94.4%)		
Age at diagnosis	12.2 ± 6.9	48.4 ± 9.8	0.60	

Table 5. Age of diagnosis vs genotype in T1DM patients

	CT	CC	p-value	OR (95 %CI)
% of genotypes	T1DM 5 (2.4%)	202 (97.6%)	0.1	1.02 (0.55–1.89)
	Control 16 (5.6%)	268 (94.4%)		
Age at diagnosis	16.8 ± 7.7	17.8 ± 8.1	0.89	

DISCUSSION

The study was motivated by the results of two meta-analyses concerning the role of HNF4A Thr130Ile variant in the development of T2DM. Jafar-Mohammadi et al. [6] found the more common Thr130Ile variant to be associated with T2DM in a meta-analysis of 14,279 cases and 26,835 controls. Although the p-values for association of Thr130Ile with T2DM in this study did not reach the threshold of significance, the odds ratios were in the same direction and of a similar magnitude for the additive model (OR 1.22; 95% CI: 0.87–1.71). Sookoian et al. [7] analyzed studies containing Thr130Ile based on 15,020 T2DM cases and 15,010 controls. They found no evidence of association of the major allele at this variant under a fixed model ($p=0.160$), although nominal significance was detected under a random model ($p=0.045$; OR=0.770 (95% CI: 0.595–0.995). Hellwege et al. [8] examined 1,270 T2DM cases and 1,017 controls and found no difference concerning HNF4A Thr130Ile variant between cases and controls, but this study analyzed a selected population of European- Americans. In the current study, similar analysis concerned the Polish population, but the results were negative, in line with the report by Hellwege. The authors, for the first time, have analyzed the relationship between HNF4A Thr130Ile variant and the development of T1DM, founding, however, no association. Thus, the role of rare variants in the development of common forms of diabetes remain to be established [9].

CONCLUSIONS

No association was found between rare variant Thr130Ile of the HNF4A gene and the development of either T2DM nor T1DM in the Polish population. The variant does not seem the affect age of diagnosis or the need for insulin therapy in T2DM patients, nor is it associated with the age of diagnosis in T1DM patients.

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